INTRODUCTION

Histones have important structural and regulatory roles mediating the dynamic packaging of DNA. The dysregulation of histone modification leads to overgrowth syndromes, such as Sotos and Weaver syndrome. Recently heterozygous variants in HIST1H1E, which encodes linker histone H1.4, has been associated with human intellectual disability. This finding might explain previously unexplained progressive decline in height percentile with age in patients with Sotos and Weaver syndrome. This finding might explain previously unexplained progressive decline in height percentile with age in patients with Sotos and Weaver syndrome.

CASE

A 11-year-old boy was referred for hypothyroidism with normal TSH. He was born at 36 weeks, with a birth weight of 3660 g (+2.37 SDS) and length of 52 cm (+1.63 SDS). There was a complaint of tiredness, weight gain, hair loss, slow growth, and tendency to sleep for two months. On examination, his height, weight, and target height were 158 cm (+1.46 SDS), 61 kg (+1.72 SDS), and 183.5 cm (+1.18 SDS), respectively. He had high anterior hairline, prominent forehead, sparse eyebrows, wide nasal bridge, hypertelorism, prominent checkbones, dental erosion, simple auriæ, fleshy hands and ears, pes planus, campodactyly, kyphoscoliosis, pectus carinatum, and mild mental retardation (Fig. 1). Repeated thyroid function tests and symptoms were consistent with central hypothyroidism. Evaluation for other pituitary functions revealed central adrenal insufficiency. Levothyroxine and hydrocortisone replacements were initiated. Although the patient was growing well with IGF1 and IGFBP3 within normal limits, very low growth hormone (GH) response to clonidine and L-dopa stimulation tests (L-dopa and clonidine stimulated peak GH: 2.13 and 3.06 mcg/l, respectively) were noted (Fig. 2). Pituitary MRI was normal. A whole exome analysis was performed and revealed a de-novo heterozygous 1bp duplication in HIST1H1E (p.Ala145Glyfs*51), which predicted a truncated protein. The duplication was located in the carboxyl-terminal domain where all previously reported variants have been located.

CONCLUSIONS

Our case is the first case of Sotos and Weaver syndrome with complete endocrine evaluation and shows hypothyroidism as a novel manifestation of this disease. This finding might explain previously unexplained progressive decline in height percentile with age in patients with Sotos and Weaver syndrome...